Notice of Allowability	Application No.	Applicant(s)	
	08/465,322	SODERLUND ET AL.	
	Examiner	Art Unit	
	Carla Myers	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to *the amendment filed July 28, 2005*.

2. ☒ The allowed claim(s) is/are *97-120*.

3. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
   a) ☐ All b) ☐ Some* c) ☐ None of the:
      1. ☐ Certified copies of the priority documents have been received.
      2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
      3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

4. ☐ A SUBSTITUTE OATH OR DECLARATION must be submitted. Note the attached EXAMINER'S AMENDMENT or NOTICE OF INFORMAL PATENT APPLICATION (PTO-152) which gives reason(s) why the oath or declaration is deficient.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   (a) ☐ including changes required by the Notice of Draftsperson's Patent Drawing Review (PTO-948) attached
      1) ☐ hereto or 2) ☐ to Paper No./Mail Date _____.
   (b) ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____.

Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).

6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☐ Notice of References Cited (PTO-892)
2. ☐ Notice of Draftperson's Patent Drawing Review (PTO-948)
3. ☐ Information Disclosure Statements (PTO-1449 or PTO/SB/08), Paper No./Mail Date _____
4. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material
5. ☐ Notice of Informal Patent Application (PTO-152)
6. ☐ Interview Summary (PTO-413), Paper No./Mail Date _____ .
7. ☐ Examiner's Amendment/Comment
8. ☒ Examiner's Statement of Reasons for Allowance
9. ☐ Other _____.

1005

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after allowance or after an Office action under *Ex Parte Quayle*, 25 USPQ 74, 453 O.G. 213 (Comm'r Pat. 1935). Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, prosecution in this application has been reopened pursuant to 37 CFR 1.114. Applicant's submission filed on October 18, 2004 has been entered.

Claim Rejections - 35 USC § 103

2. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 97-106 and 117 are rejected under 35 U.S.C. 103 as being unpatentable over Mills (U.S. Patent No. 5,221,518) in view of Dattagupta (EP 0297379; cited in the IDS of 9/8/1995).

Mills teaches methods for sequencing DNA wherein the methods require the use of the reagents of a primer, a polymerase and an admixture comprising labeled A, T, C and G deoxynucleotides and A, T, C and G chain-terminating nucleotide analogues (see, e.g., columns 26, 36 and 54-55). In the method of Mills, the nucleotide sequence to be determined is at a position immediately adjacent to or a plurality of nucleotides away from the 3' terminus of the primer (column 44). Mills teaches that the nucleotides are labeled using, for example, a radioactive or mass label. At column 44, Mills further teaches that the nucleotides can be labeled with fluorescent moieties, stating that the "The relative amounts of each base can be quantified by absorbance, fluorescence or by scintillation quantification if the nucleotides or bases are radiolabeled." It is noted that the present claims recite kits containing chain-terminating nucleotide analogues and as such the claims are considered to include chain-terminating nucleotides that are labeled with a radioactive, mass or fluorescent label.

Accordingly, the method of Mills requires the use of the reagents of a primer, wherein the primer hybridizes adjacent to or within a distance of a plurality of nucleotides to the nucleotide to be detected, a DNA or RNA polymerase (i.e., an enzymatic polymerizing reagent), and an admixture of labeled deoxynucleotides and at least two different chain-terminating nucleotide analogues. Mills does not teach packaging the reagents required to practice the sequencing method in a kit.

However, reagent kits for performing nucleic acid analysis methods were conventional in the field of molecular biology at the time the invention was made. In particular, Dattagupta (column 3) teaches packaging reagents such as primers,

nucleotides and polymerizing enzymes in a kit. In view of the conventionality of kits and the disclosure of Dattagupta, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have packaged the primer, polymerizing agent, and an admixture of labeled dNTPs and at least two different chain-terminating nucleotide analogues in a kit for the expected benefits of convenience and cost-effectiveness for practioners in the art wishing to perform the disclosed method of sequencing target nucleic acids.

With respect to claim 99, Mills does not specifically teach the use of primers that are 10-40 nucleotides in length. However, Dattagupta teaches that the primers used for primer extension reactions may be of a length of about 5-100 bases (columns 4-5). Dattagupta teaches that the length of the primer should be selected so as to allow for the specific annealing of the primer to the target nucleic acid under the temperature and reaction conditions in which the annealing and extension steps are performed. Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have used primers of a length of about 10-40 nucleotides in the method of Mills and to have packaged these primers in a kit because use of primers of about 10-40 nucleotides were conventional in the art, as taught by Dattagupta, and the use of such primers would have provided an effective means for performing the sequencing method of Mills under reaction conditions that favored the annealing and extension of 10-40mer primers.

With respect to claims 105 and 106, Mills does not teach amplifying the target nucleic acids by PCR, particularly using a primer comprising an attachment moiety.

However, Dattagupta teaches methods for amplifying a target nucleic acid using primers comprising an attachment moiety (see, e.g., column 4). Dattagupta (column 4) teaches that the primers comprising an attachment moiety may be immobilized prior to or following PCR amplification. As taught by Dattagupta, the use of immobilizable primers provides the advantage that the amplification products can be easily separated from the reaction mixture and then used for further analysis.

In view of the teachings of Dattagupta, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Mills so as to have amplified the target nucleic acid by PCR prior to performing the sequencing reaction in order to have provided the advantage of increasing the quantity of the target nucleic acid, thereby increasing the sensitivity of the sequencing method. Further, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have used primers containing an attachment moiety for immobilizing the primers to a solid support because this would have provided a convenient means for immobilizing the primers to a solid support prior to or following the amplification reaction and thereby would have facilitated the separation of the amplification products form the reaction mixture. Modification of the method of Mills as stated above would have resulted in a method that required the use of the reagents of a primer, wherein the sequencing primer hybridizes adjacent to or within a distance of a plurality of nucleotides to the nucleotide to be detected, a DNA or RNA polymerase (i.e., an enzymatic polymerizing reagent), an admixture of labeled dNTPs and at least two different chain-terminating nucleotide analogues, amplification primers comprising an

attachment moiety and a solid support. In view of the conventionality of kits and the teachings of Dattagupta of packaging assay reagents in a kit, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have packaged said reagents in a kit for the benefits of convenience and cost-effectiveness for practioners wishing to perform the modified sequencing method.

With respect to claim 98, Mills does not teach sequencing primers that comprise an attachment moiety. However, as discussed above, Dattagupta teaches performing primer extension reactions using primers comprising an attachment moiety. Dattagupta (column 4) teaches that immobilizing the primers prior to or following primer extension allows for the easy separation of amplification products from the reaction mixture. Further, Mills (e.g., columns 26-27) teaches that it is desirable to separate the extension products from the reaction mixture prior to further sequence analysis. Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Mills so as to have used a sequencing primer comprising an attachment moiety in order to have provided an effective and rapid means for capturing and separating the sequencing products from the reaction mixture. Further, one of ordinary skill in the art at the time the invention was made would have been motivated to have included the sequencing primer comprising an attachment moiety in the kit in order to have generated a kit that facilitated the capture and separation of the primer extension products and which thereby facilitated the method of Mills for determining the sequence of a nucleic acid.

3. The art made of record and not relied upon is considered pertinent to applicant's disclosure.

A. Holmes et al (WO 89/09282; cited in the IDS of 9/8/95; pages 11-12) discloses methods for sequencing DNA wherein the methods require the use of an admixture that consists of dCTP, dGTP, dTTP and ddATP. During the sequencing reaction, this admixture is added to a solution containing labeled dATP. However, Holmes does not teach or suggest labeling the ddNTP in place of the dNTP. Also, Holmes does not teach an admixture containing at least two different ddNTPs.

B. Skinner (cited in the IDS of 10/18/04) teaches methods in which the misincorporation of nucleotides by AMV reverse transcriptase is studied. In one experiment (see page 6958), Skinner teaches primer extension reactions using a labeled primer together with an admix of dGTP and ddATP. However, Skinner does not teach or suggest or provide the motivation to label the ddATP in place of the primer.

C. Cohen (EP 0412883, published 2-13-91 and FR 2650840; cited in the IDS) disclose methods of sequencing a nucleic acid using an admixture of labeled ddATP, ddCTP, ddGTP and ddTTP. Cohen does not teach methods which require an admixture of both dNTPs and ddNTPs.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Carla Myers whose telephone number is (571) 272-0747. The examiner can normally be reached on Monday-Thursday from 6:30 AM-5:00 PM. A message may be left on the examiner's voice mail service. If attempts to reach

the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (571)-272-0745.

The fax phone number for the organization where this application or proceeding is assigned is (571)-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at (866)-217-9197 (toll-free).

Carla Myers
January 19, 2005

REASONS FOR ALLOWANCE

The following is an examiner's statement of reasons for allowance:

The prior art of Mills teaches methods for sequencing DNA wherein the methods require the use of the reagents of a primer, a polymerase and an admixture comprising labeled A, T, C and G deoxynucleotides (dNTP) and A, T, C and G chain-terminating nucleotide analogues (i.e., ddNTPs; see columns 26, 36 and 54-55). In the method of Mills, the nucleotide sequence to be determined is at a position immediately adjacent to or a plurality of nucleotides away from the 3' terminus of the primer (column 44). Accordingly, the method of Mills requires the use of each of the 4 dNTPs and each of the 4 ddNTPs. Mills does not teach or suggest methods in which **each of the dNTPs** is complementary to a nucleotide which differs from **any nucleotide** to which a chain-terminating nucleotide is complementary.

It is noted that the present claims are drawn to kits, wherein the kits are characterized (in part) as comprising "a plurality of nucleoside triphosphates...each deoxynucleotide of said plurality of nucleoside triphosphates being complementary to a nucleotide which differs from any nucleotide to which a chain-terminating nucleotide analogue of said plurality of nucleoside triphosphates is complementary." As such, the claims necessarily exclude within the kit (that is, within the defined "plurality of nucleoside triphosphates" or elsewhere) the presence of any nucleoside triphosphate which is complementary to a nucleotide to which the chain-terminating nucleotide analogue is complementary. For example, the claims exclude kits comprising both dATP and ddATP. Additionally, it is noted that the recitation in claims 97-106 and 119 of

"at least two different chain-terminating nucleotide analogues" has been interpreted to mean that the chain-terminating nucleotide analogues are different from one another (for example, the "at least two different chain-terminating nucleotide analogues" may be ddATP and ddCTP).

Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Carla Myers whose telephone number is (571) 272-0747. The examiner can normally be reached on Monday-Thursday from 6:30 AM-5:00 PM. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (571)-272-0745.

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Carla Myers
October 5, 2005

CARLA J. MYERS
PRIMARY EXAMINER